



[Billing Code 4140-01-P]

## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: State of the Science and the Path Forward**

**AGENCY:** Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH)

**ACTION:** Announcement of a Workshop; Call for Abstract Submissions

**SUMMARY:** The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces an “International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: State of the Science and the Path Forward.” This workshop, the third in a series of specialized vaccine workshops, will review new methods and approaches for acellular pertussis (aP) vaccine safety testing that incorporate innovations in science and technology. These scientific innovations should improve test accuracy, precision, and efficiency while also reducing or replacing the use of animals in vaccine safety testing. The goal is to address the path toward global validation, acceptance, and implementation of scientifically valid alternative methods for aP vaccines.

The workshop is open to the public at no charge with attendance limited only by the available space; however, advance registration is required (see DATES). NICEATM also invites submission of abstracts for scientific posters for display at the workshop (see SUPPLEMENTARY INFORMATION).

**DATES:** The workshop is scheduled for November 28–29, 2012. Sessions will begin each day at 8:00 a.m. and will end each day at approximately 5:45 p.m. The deadline for registration is November 16, 2012. The deadline for submission of poster abstracts is October 12, 2012.

**ADDRESSES:** The workshop will be held at the William H. Natcher Conference Center, 45 Center Drive, NIH Campus, Bethesda, MD 20892. Individuals with disabilities who need accommodation to participate in this event should contact Ms. Debbie McCarley at voice telephone: 919-541-2384 or email: [mccarley@niehs.nih.gov](mailto:mccarley@niehs.nih.gov). TTY users should contact the Federal TTY Relay Service at 800-877-8339. Requests should be made at least 5 business days in advance of the event.

**FOR FURTHER INFORMATION CONTACT:** Dr. William S. Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2–16, Research Triangle Park, NC, 27709, (telephone) 919-541-2384, (fax) 919-541-0947, (email) [niceatm@niehs.nih.gov](mailto:niceatm@niehs.nih.gov). Courier address: NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

## **SUPPLEMENTARY INFORMATION:**

### **Background**

Pertussis, also known as whooping cough, is a highly contagious disease caused by the bacterium *Bordetella pertussis*. Pertussis was one of the most common childhood diseases of the early 20<sup>th</sup> century and was once a major cause of childhood mortality in the United States. A whole-cell vaccine introduced in the 1940s reduced the incidence of pertussis by more than 80%. aP vaccines, which became available in the 1980s, were developed in response to public concern with some common side effects (e.g., fever, swelling at injection site) and rare serious events that coincided with the use of whole-cell pertussis vaccines. These new generation aP vaccines contain different combinations of the putative protective antigens of *B. pertussis* bacteria (e.g.,

inactivated pertussis toxin [PTx/d], pertactin, and fimbriae) and are less reactogenic than whole-cell vaccines.

Regulatory authorities require safety, potency, and purity testing prior to the release of each production lot of pertussis or pertussis antigen-containing vaccines. The murine histamine sensitization test (HIST) is a key safety test used to monitor residual levels of pertussis toxin (PTx) in vaccines. This test is performed to ensure that PTx has been effectively inactivated before release of vaccines (Corbel and Xing, 2004). However, such testing may involve large numbers of mice, some of which can experience significant unrelieved pain and distress. In addition, the HIST has technical challenges requiring frequent retesting, thereby increasing vaccine testing expense and animal usage. An international workshop organized in 2010<sup>1</sup> by NICEATM, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and their international partners identified the HIST as a priority for future research, development, and validation of alternative test methods that could further reduce, refine (enhance animal well-being and lessen or avoid pain and distress), or replace animal use for aP vaccine safety testing (Stokes *et al.*, 2011).

Two international workshops reviewed currently available alternative *in vitro* assays to the HIST and discussed a path forward to achieve their validation and adoption<sup>2,3</sup>. The Workshop on Animal-Free Detection of PTx in Vaccines – Alternatives to HIST was held on June 9 and 10, 2011, at the Paul Ehrlich Institute, Germany. An International Working Group for Alternatives to HIST (previously designated as the “Spiked-vaccine Working Group”) was

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<sup>1</sup> International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions, Bethesda, MD, USA September 14-16, 2010

<sup>2</sup> Workshop on Animal-Free Detection of PTx in Vaccines – Alternatives to HIST, Langen, Germany, June 9-10, 2011

<sup>3</sup> Alternative Safety Testing Strategies for Acellular Pertussis Vaccines (8<sup>th</sup> World Congress Satellite meeting), Montreal, Canada, August 21, 2011

organized to coordinate future studies on relevant alternative methods (Bache *et al.*, 2012; Isbrucker, 2011)

The Alternative Safety Testing Strategies for Acellular Vaccines Workshop was held on August 21, 2011, as a satellite meeting to the 8th World Congress on Alternatives and Animal Use in the Life Sciences in Montreal, Canada (Isbrucker, 2011). Participants at this workshop further discussed and clarified regulatory agency requirements to achieve the acceptance of alternative methods to the HIST and agreed that conducting a study using spiked vaccines to compare the sensitivities of the HIST and *in vitro* assays would be important.

Several *in vitro* assays have been developed, or are currently under development, with the aim of finding an alternative method to the HIST for monitoring residual PTx activity in aP vaccines. The International Working Group for Alternatives to HIST is coordinating the acquisition and distribution of aP vaccine samples from manufacturers to research laboratories for generation of data using *in vitro* methods to evaluate vaccines spiked with a known amount of PTx. Data from the various alternative assays will be presented at the upcoming workshop and will form the basis for identifying *in vitro* methods for future assessment in the next international collaborative study.

The following methods will be evaluated and may be used to generate data to be presented at the upcoming workshop:

1. Binding assay: used to assess the amount of PTx/toxoid binding activity to the glycoprotein fetuin
2. Enzymatic assay: monitors the residual ADP-ribosylation of the PTx/toxoid
3. Cell-based assays: monitor the generation of cAMP or decrease in cellular ATP following exposure to PTx

#### 4. Genetic assays: determine potential genomic markers of PTx activity

This workshop will provide a forum to discuss and review the *in vitro* protocols and available data from the International Working Group for Alternatives to HIST study and will suggest future collaborative projects using prepared materials. The workshop will also review additional new methods and approaches for aP vaccine safety testing that should improve test accuracy, precision, and efficiency while also reducing or replacing the use of animals in vaccine safety testing. Finally, the workshop will address the path toward global validation, acceptance, and implementation of scientifically valid alternative methods for aP vaccines.

#### **Preliminary Workshop Agenda and Registration**

Registration information, draft agenda, and additional meeting information are available on the NICEATM–ICCVAM website (<http://iccvam.niehs.nih.gov/meetings/HISTWksp-2012/HISTWksp.htm>) and upon request from NICEATM (see FOR FURTHER INFORMATION CONTACT).

#### **Call for Abstract Submissions**

NICEATM and ICCVAM invite the submission of abstracts for scientific posters to be displayed during this workshop. Guidelines for the submission of abstracts are available at <http://iccvam.niehs.nih.gov/meetings/HISTWksp-2012/HISTWksp-AbstractSubmit-508.pdf>. Abstracts must be submitted by email to [niceatm@niehs.nih.gov](mailto:niceatm@niehs.nih.gov). The deadline for abstract submission is October 12, 2012. The corresponding author will be notified regarding the abstract's acceptance within 21 working days of the submission deadline. Guidelines for poster presentations will be sent to the corresponding author with notification of acceptance.

## **Background Information on NICEATM and ICCVAM**

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information. ICCVAM conducts technical evaluations of new, revised, and alternative safety testing methods and integrated testing strategies with regulatory applicability and promotes the scientific validation and regulatory acceptance of testing methods that more accurately assess the safety and hazards of chemicals and products and that reduce, refine, or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM, provides scientific and operational support for ICCVAM-related activities, and conducts independent validation studies to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. NICEATM and ICCVAM welcome the public nomination of new, revised, and alternative test methods and strategies applicable to the needs of U.S. Federal agencies. Additional information about ICCVAM and NICEATM can be found on the NICEATM–ICCVAM website (<http://iccvam.niehs.nih.gov>).

## **References**

- Bache C, Hoonakker M, Hendriksen C, Buchheit K-H, Spreitzer I, Montag T. 2012. Workshop on Animal Free Detection of Pertussis Toxin in Vaccines – Alternatives to the Histamine Sensitization Test. *Biologicals* 40: 309-311.
- Corbel MJ, Xing DK-L. 2004. Toxicity and potency evaluation of pertussis vaccines. *Exp Rev Vaccines* 3: 89-101.
- Isbrucker R. 2011. Alternative safety testing strategies for acellular pertussis vaccines. *ALTEX Proceedings*, 1/12, Proceedings of WC8; 77-80.

Stokes WS, Kulpa-Eddy J, McFarland RM. 2011. The International Workshop on Alternative Methods to Reduce, Refine and Replace the Use of Animals in Vaccine Potency and Safety Testing – Introduction and Summary. In: International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (Kulpa-Eddy J, McFarland R, Stokes WS, eds). Procedia Vaccinol 5: 1-15.

Dated: August 20, 2012

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[FR Doc. 2012-21368 Filed 08/28/2012 at 8:45 am; Publication Date: 08/29/2012]